Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Jaffe GJ, Dick AD, Brézin AP, et al. Adalimumab in patients with active noninfectious uveitis. N Engl J Med 2016;375:932-43. DOI: 10.1056/NEJMoa1509852

Appendix

Methods

Study sites

The study was conducted at 67 clinical sites in Australia, Canada, Europe, Israel, Latin America, and the United States.

Sample size determination

Assumed treatment failure rates at 6 months were 70% for placebo and 50% for adalimumab. A conservative assumption was that treatment failures would begin to occur after 2 months because of prednisone taper. A pooled dropout rate of 35% over 12 months was also assumed. Based on these assumptions, 138 treatment failures were sufficient for a 2-sided significance level of 5% using a log-rank test. This calculation assumed power of 90% and an average accrual rate of 4 patients per month in the first 30 months and 7 patients per month thereafter.

A series of calculations with different sample sizes using the event rate, recruitment rate, and dropout rate assumptions described above was performed using East5, v5.2.00 (Cytel Inc., Cambridge, MA). To achieve 138 treatment failure events, it was determined that a sample size of approximately 234 patients was needed.

Stopping guidelines

Patients received treatment and were followed for 80 weeks or until the 138th treatment failure occurred.

Randomization

An interactive voice/web response system was used to determine the randomization of patients. Eligible patients were randomized in a 1:1 double-masked fashion to adalimumab or placebo using baseline immunosuppressant treatment as the stratification factor. Randomization was performed using an adequate block size.

Masking

This was a double-masked study. All sponsor personnel with direct oversight of the conduct and management of the study (with the exception of those providing study treatments), investigators, study site personnel, and patients were masked to treatment. Masking was maintained throughout the 80-week treatment period.

Sample collection and analysis of anti-adalimumab antibodies

Blood samples for the measurement of anti-adalimumab antibodies (AAA) were collected at baseline and at study weeks 12, 27, 36, and 52, or at the early termination visit for patients who discontinued the study before week 52. Serum AAA concentrations were measured using a validated, enzyme-linked immunosorbent assay method.[1] Serum samples were considered to be positive for AAA (AAA^+) if AAA concentration was >20 ng/mL (confirmed with confirmatory assay) in any sample collected within 30 days after an adalimumab dose. Patients with ≥1 AAA^+ sample were considered to be AAA^+.

Statistical analysis of secondary endpoints

Testing of ranked secondary endpoints was conducted in hierarchical order and stopped if an endpoint returned a nonsignificant result; post hoc analyses were performed, and nominal *P*

values for between-group differences were provided. Changes in anterior chamber cell grade, vitreous haze grade, best corrected visual acuity, and central retinal thickness were compared between groups by analysis of variance adjusted for clustered observations within a patient. Central retinal thickness analysis used the optical coherence tomography (OCT) machine type as an additional factor. Time to OCT evidence of cystoid macular edema on or after week 6 was compared between groups with a log-rank test in which patients without pre-existing cystoid macular edema at baseline were included. In a post hoc analysis, macular edema was defined by retinal thickening depending on the OCT machine type used (Stratus, ≥260 μm; Cirrus, ≥320 μm; Spectralis, ≥340 μm), and only patients without macular edema, macular holes, or retinal detachment at baseline were included. Changes in Visual Functioning Questionnaire-25 composite score and subscores were compared between groups by analysis of variance with treatment as a factor. For analysis of secondary variables, with the exception of time to OCT evidence of macular edema, patients lost to follow-up on or before week 6 were excluded from the analysis, and missing data were imputed using last observation carried forward.

Author disclosures

GJJ has served as a consultant for AbbVie. ADD has served on advisory boards for AbbVie. APB has served on advisory boards and as a consultant for AbbVie. QDN has served on the scientific advisory boards for AbbVie, Santen, XOMA, and Bausch & Lomb, and chairs the steering committee for the VISUAL studies. JET has served on advisory boards for AbbVie, Mallinckrodt, and XOMA, as a consultant for Gilead, and has received research support from NEI and Allergan Inc. TB-A has served on scientific advisory boards for AbbVie. AH has received research support from AbbVie, Pfizer, Novartis, and Deutsche Forschungsgemeinschaft, and has received study fees from AbbVie, Alimera Sciences, Allergan, Santen, and XOMA. DS has served on the AbbVie steering committee. DSC has served as a consultant for XOMA, Aldeyra, and Biogen Idec, and has received research support from AbbVie, Allergan, Novartis, and Santen. EBS has served on the AbbVie steering committee, as a consultant for AbbVie, XOMA, and Santen, and has received research support from AbbVie, Bristol-Myers Squibb, EyeGate, and Genentech. AC, NVK, APS, MK, and ST are employees of AbbVie. PK and PF have no conflicts of interest to declare.

Additional study investigators

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Table S1. Inclusion and Exclusion Criteria

Inclusion Criteria
1. Patient age, ≥18 years
2. Diagnosed with non-infectious intermediate, posterior, or panuveitis
3. Active disease at the baseline visit as defined by the presence of ≥1 of the following parameters in at least 1 eye despite ≥2 weeks of maintenance therapy with oral prednisone (≥10 mg/day to ≤60 mg/day) or oral corticosteroid equivalent: • Active, inflammatory, chorioretinal and/or inflammatory retinal vascular lesion • ≥2+ anterior chamber cell grade (Standardization of Uveitis Nomenclature criteria) • ≥2+ vitreous haze grade (National Eye Institute [NEI]/Standardization of Uveitis Nomenclature criteria)
4. Using oral prednisone at a dose of ≥10 mg/day to ≤60 mg/day (or oral corticosteroid equivalent) for ≥2 weeks before screening, with no dosing change from screening to baseline visit
5. If female, either not of childbearing potential (postmenopausal for ≥1 year or surgically sterile due to bilateral tubal ligation, bilateral oophorectomy, and/or hysterectomy) or of childbearing potential and practicing an approved method of birth control (condoms, sponge, foams, jellies, diaphragm, or intrauterine device; hormonal contraceptives for 90 days before study drug administration; or a vasectomized partner) throughout the study and for 150 days after the last dose of study drug
6. Judged to be in good health as determined by the principal investigator based on the results of medical history, laboratory profile, physical examination, chest x-ray, and a 12-lead electrocardiogram performed during screening

7. Able and willing to self-administer subcutaneous injections or have a qualified person available to administer subcutaneous injections

8. Able and willing to provide written informed consent and comply with the requirements of the study protocol

9. No previous, active, or latent tuberculosis. Only 1 tuberculosis test was allowed and required for patient eligibility. Patients with a repeat indeterminate QuantiFERON-TB Gold test (or interferon-gamma release assay [IGRA] equivalent) were not eligible. A repeat QuantiFERON-TB Gold test (or IGRA equivalent) was not permitted if the purified protein derivative (PPD) skin test was positive. The tuberculosis screening tests were diagnostic tests. In the event of a negative tuberculosis screening test, the results were to be interpreted in the context of the patient's epidemiology, history, exam findings, etc, and it was the responsibility of the investigator to determine if a patient had previous, active, or latent tuberculosis or not. Under no circumstances could a patient with a positive PPD result or positive QuantiFERON-TB Gold test (or IGRA equivalent) enter the study.

10. Documented prior adequate response to oral corticosteroids (equivalent of oral prednisone up to 1 mg/kg/day)

Exclusion Criteria

1. Isolated anterior uveitis

2. Prior inadequate response to high-dose oral corticosteroids

3. Confirmed or suspected infectious uveitis, including but not limited to infectious uveitis due to tuberculosis, cytomegalovirus, Lyme disease, toxoplasmosis, human T-lymphotropic virus type 1 infection, Whipple disease, herpes zoster virus, or herpes simplex virus

4. Presumed ocular histoplasmosis syndrome

5. Ocular masquerade syndromes such as ocular lymphoma

6. Serpiginous choroidopathy

7. Contraindication to pupil dilation with mydriatic eye drops

8. Corneal or lens opacity that would preclude visualization of the fundus or that would likely require cataract surgery during the trial

9. Intraocular pressure ≥25 mmHg and on ≥2 glaucoma medications, or evidence of glaucomatous optic nerve injury

10. Best corrected visual acuity <20 Early Treatment Diabetic Retinopathy Study letters in at least 1 eye at baseline

11. Intermediate uveitis or panuveitis with signs of intermediate uveitis (eg, presence or history of snowbanking or snowballs) and symptoms or magnetic resonance imaging (MRI) findings suggestive of a demyelinating disease such as multiple sclerosis. All patients with intermediate uveitis or panuveitis with signs of intermediate uveitis were required to have a brain MRI within 90 days before baseline.

12. Previous exposure to anti–tumor necrosis factor (TNF) therapy or any biologic therapy (except intravitreal anti–vascular endothelial growth factor [VEGF] therapy) with a potential therapeutic impact on non-infectious uveitis

13. Using >1 immunosuppressive therapy (not counting corticosteroids) at baseline

14. Using concomitant immunosuppressive therapy at baseline other than methotrexate, cyclosporine, mycophenolate mofetil or an equivalent drug (eg, mycophenolic acid), azathioprine, or tacrolimus

15. If entering the study on 1 concomitant immunosuppressive therapy, dose had been increased within the last 28 days before baseline or was not within the following allowable doses at

baseline:

- Methotrexate ≤25 mg per week
- Cyclosporine ≤4 mg/kg per day
- Mycophenolate mofetil ≤2 g per day or an equivalent drug to mycophenolate mofetil at an equivalent dose approved by the medical monitor
- Azathioprine ≤175 mg per day
- Tacrolimus (oral formulation) ≤8 mg per day

16. Prior or current use of chlorambucil

17. Received Retisert (glucocorticosteroid implant) within 3 years before baseline or had complications related to the device

18. Received intraocular or periocular corticosteroids within 30 days before baseline

19. History of prior ocular surgery within 90 days before baseline with the exception of refractive laser surgery, retinal laser photocoagulation, or neodymium-doped yttrium aluminium garnet posterior capsulotomy. These 3 exceptions were exclusionary within 30 days before baseline.

20. Planned (elective) eye surgery within 80 weeks after baseline

21. Proliferative or severe non-proliferative diabetic retinopathy or clinically significant macular edema due to diabetic retinopathy

22. Neovascular/wet age-related macular degeneration

23. Abnormality of vitreoretinal interface (i.e., vitreomacular traction, epiretinal membranes) with the potential for macular structural damage independent of the inflammatory process

24. Systemic inflammatory disease requiring continued therapy with oral corticosteroids or a prohibited immunosuppressive agent at screening or baseline

25. Treatment with any investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever was longer) of the drug before baseline

26. Prior exposure to biologics that have a potential or known association with progressive multifocal leukoencephalopathy (i.e., Tysabri [natalizumab], Rituxan [rituximab], or Raptiva [efalizumab])

27. Infection requiring treatment with intravenous anti-infectives within 30 days before baseline or oral anti-infectives within 14 days before baseline

28. History of moderate to severe congestive heart failure (New York Heart Association class III or IV), recent cerebrovascular accident, or any other condition that, in the opinion of the investigator, would put the patient at risk by participation in the protocol

29. History of demyelinating disease (including myelitis and optic neuritis) or neurologic symptoms suggestive of demyelinating disease including but not limited to optic neuritis

30. Patients with chronic recurring infections, active tuberculosis result at screening or a history of invasive infection (e.g., listeriosis, histoplasmosis), or HIV. In Argentina and Mexico, a negative HIV test was required.

31. Known hypersensitivity to adalimumab or its excipients

32. Positive pregnancy test at screening or baseline

33. Female subjects who are breastfeeding or considering becoming pregnant during the study

34. Evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell, basal cell carcinoma, or localized carcinoma in situ of the cervix

35. History of clinically significant drug or alcohol abuse in the last 12 months

36. Considered by the investigator, for any reason, to be an unsuitable candidate for the study

37. Clinically significant abnormal screening laboratory results as evaluated by the investigator

38. Positive syphilis test (fluorescent treponemal antibody)

39. Not in compliance with restrictions regarding prior and concomitant therapy

40. Severe vitreous haze that would preclude visualization of the fundus at baseline

41. Received Ozurdex (dexamethasone implant) within 6 months before baseline

42. Received intravitreal methotrexate within 90 days before baseline

43. Received intravitreal anti-VEGF therapy:

- Within 45 days of the baseline visit for Lucentis (ranibizumab) or Avastin (bevacizumab)
- Within 60 days of baseline for anti-VEGF Trap (aflibercept)

44. History of marijuana use, including medical or recreational marijuana, in the past 12 months

45. Hepatitis B: HBsAg positive or detection at or above level of sensitivity on the HBV-DNA PCR qualitative test for HBcAb, total, and/or HBsAb-positive subjects

46. Presence of an active systemic viral infection or any active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study

47. Use of a systemic carbonic anhydrase inhibitor within 1 week before screening

48. Macular edema as the only sign of uveitis

49. History of scleritis

50. Patients requiring tuberculosis prophylaxis

51. Intolerance to high-dose oral corticosteroids (equivalent of oral prednisone 1 mg/kg/day or 60–80 mg/day)

52. Use of cyclophosphamide within 30 days before baseline

Table S2. Oral Prednisone Burst and Taper Schedule*

Study Week	Prednisone Dose, mg/day
Burst, week 0	60.0
Taper	
1	60.0
2	50.0
3	40.0
4	30.0
5	20.0
6	15.0
7	12.5
8	10.0
9	7.5
10	5.0
11	4.0
12	3.0
13	2.0
14	1.0
15	Discontinue prednisone

*All patients entering the study were placed on a dose of 60 mg/day at the baseline visit. The schedule mandated discontinuation of corticosteroid therapy by week 15. No deviations from the taper schedule were allowed.

Table S3. Schedule of Study Procedures

	Study Visit				
Procedure	**Screening**	**Baseline**	**On-Therapy Weeks 1 Through 76***	**Final Visit or Early Termination**	**Unscheduled**
VFQ-25[†]	–	X	X	X	X
best corrected visual acuity	X	X	X	X	X
Slit-lamp exam	X	X	X	X	X
OCT	X	X	X	X	X
Dilated indirect ophthalmoscopy	X	X	X	X	X
Monitor AEs[‡]	X	X	X	X	X
Monitor concomitant medication	X	X	X	X	X

AE=adverse event; OCT=optical coherence tomography; VFQ-25=Visual Functioning Questionnaire-25.

*Study visits were scheduled at weeks 1, 4, 6, and 8, and every 4 weeks thereafter with the exception that there was no study visit at week 28; the study visit was scheduled for week 27. The visit window for all scheduled visits was ±3 days through week 6 and ±7 days after week 6.

[†]Questionnaire was administered by site staff (interview administered) before any other study procedure or examination.

[‡]AEs were also collected up to 70 days after the last injection or until rollover into a separate extension study.

Table S4. Extent of Exposure to Topical Corticosteroids

Exposure to Topical Corticosteroids	Placebo (n=37)	Adalimumab (n=30)
Total doses received, n		
Mean ± SD	83.5±94.6	93.9±113.1
Median	50	67
Range	7–505	7–513
Duration of treatment,* days		
Mean ± SD	27.4±17.4	31.1±23.6
Median	27	28
Range	7–92	7–120
Duration of exposure, days; n (%)		
1–14	8 (21.6)	8 (26.7)
15–28	16 (43.2)	8 (26.7)
29–42	8 (21.6)	9 (30.0)
43–56	2 (5.4)	1 (3.3)
57–70	2 (5.4)	3 (10.0)
>70[†]	1 (2.7)	1 (3.3)

*Duration of treatment reflects last dose date minus first dose date plus 1 day.
[†]Placebo, 92 days; adalimumab, 120 days.

Table S5. Exploratory Analyses of Secondary Efficacy Variables 5-9 (Intent-to-Treat Population)

	Placebo (n=107)		Adalimumab (n=110)	
Secondary Variable*	**n**	**Mean**	**n**	**Mean**
5. Percent change in central retinal thickness[§]				
Left eye	100	20.2	100	9.6
Right eye	102	22.0	101	8.2
Difference, mean (95% CI)		–11.4 (–20.9 to –1.8)		
6. Change in VFQ-25 total score[‖]	102	–5.50	101	–1.30
Difference, mean (95% CI)		4.20 (1.02 to 7.38)		
7. Change in VFQ-25 distance vision subscore[‖]	102	–5.64	101	–3.77
Difference, mean (95% CI)		1.86 (–2.03 to 5.75)		
8. Change in VFQ-25 near vision subscore[‖]	102	–8.09	101	–2.97
Difference, mean (95% CI)		5.12 (0.34 to 9.90)		
9. Change in VFQ-25 ocular pain subscore[‖]	102	–12.62	101	–2.60
Difference, mean (95% CI)		10.02 (4.86 to 15.19)		

*Data reflect change from best state achieved before week 6 to the final or early termination visit.

VFQ-25=Visual Functioning Questionnaire-25

[§]*P* value for between-group differences from analysis of variance with treatment and OCT machine as factors, adjusted for clustered observations; percent change in central retinal thickness, *P*=0.02. This *P* value is considered exploratory and descriptive in nature.

[‖]*P* value for between-group differences from analysis of variance with treatment as a factor; change in VFQ-25 total score, *P*=0.010; change in VFQ-25 distance vision subscore, *P*=0.35; change in VFQ-25 near vision subscore, *P*=0.04; change in VFQ-25 ocular pain subscore, *P*<0.001. This *P* value is considered exploratory and descriptive in nature.

Figure S1. Patient Disposition.

*Includes patients who experienced treatment failure or reached 80 weeks of treatment without treatment failure. †Some patients had multiple reasons for discontinuation; total counts for reasons for discontinuation exceed the total number of discontinuations.

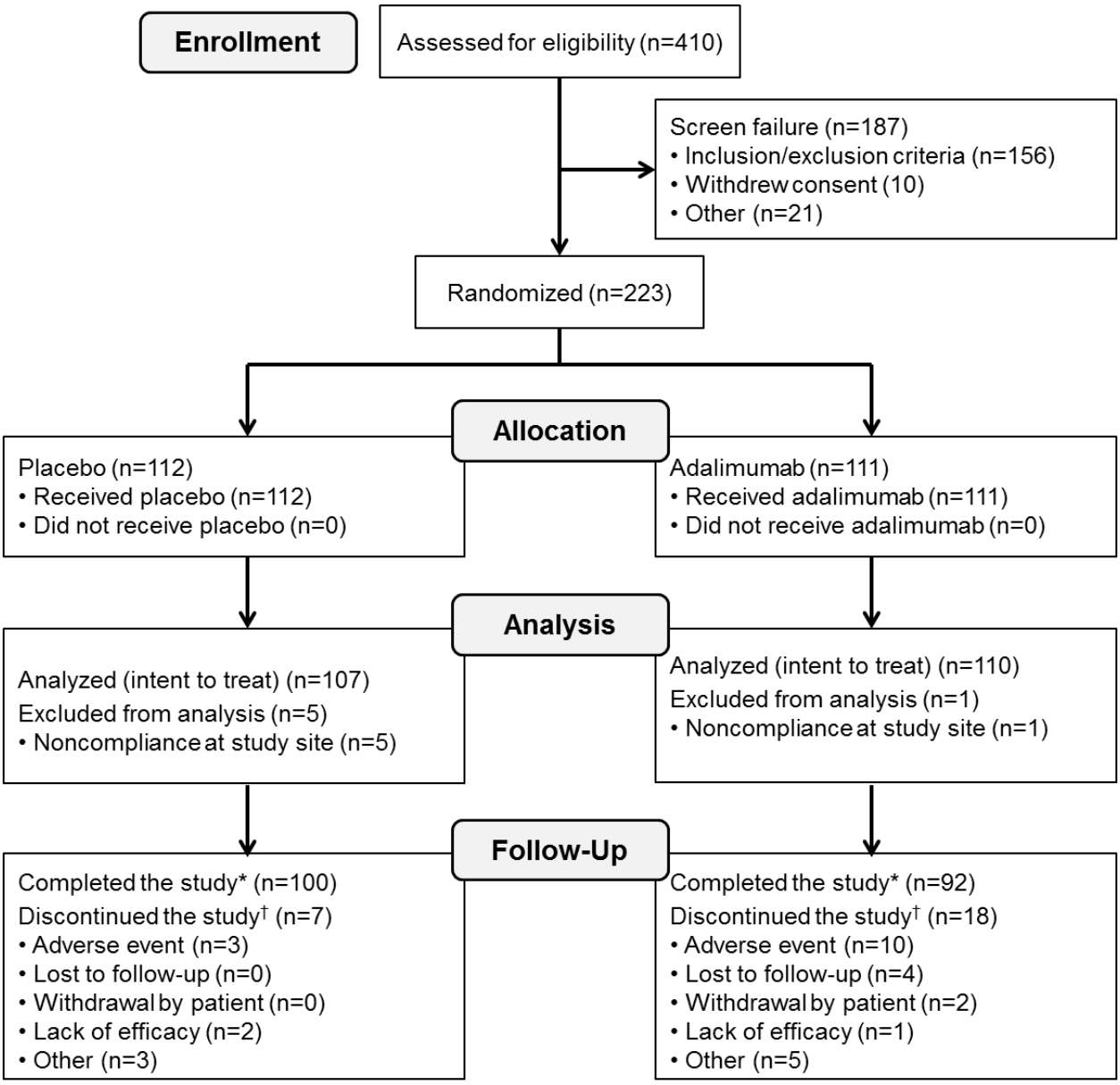
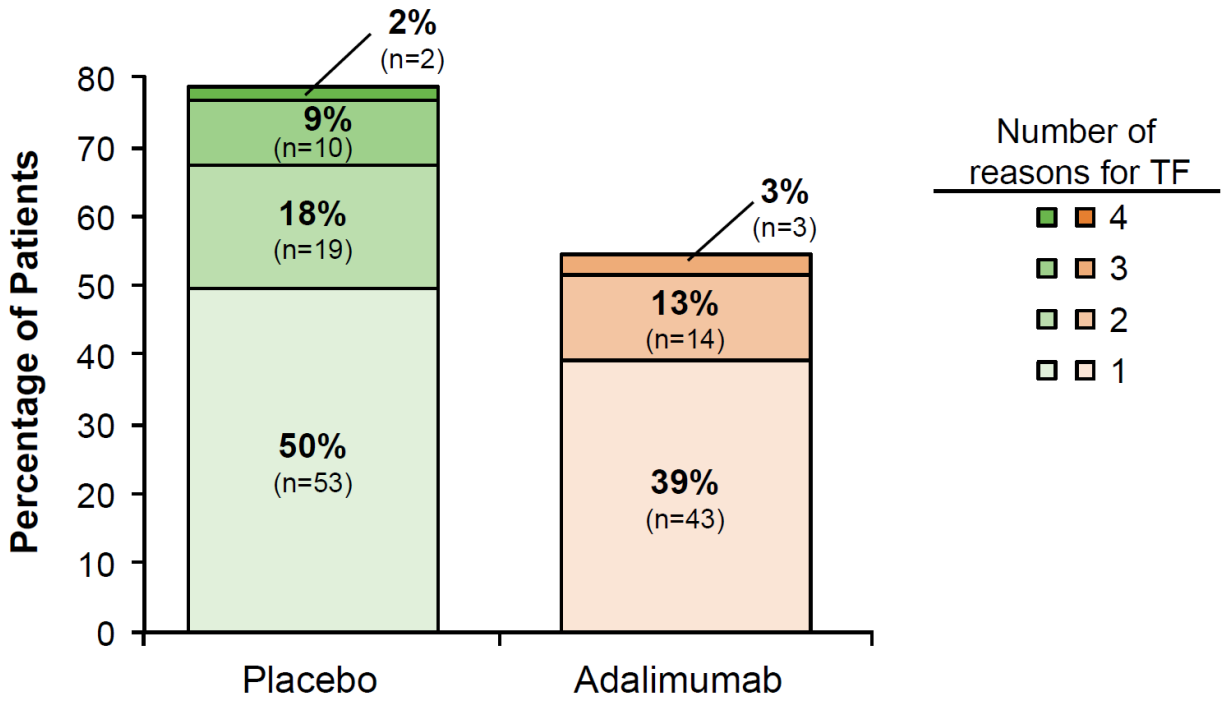


Figure S2. Number of Reasons for Treatment Failure Per Treatment Group. Percentages of patients are indicated within bars.



References

1. Sharma S, Eckert D, Hyams JS, et al. Pharmacokinetics and exposure-efficacy relationship of adalimumab in pediatric patients with moderate to severe Crohn's disease: results from a randomized, multicenter, phase-3 study. Inflamm Bowel Dis 2015;21:783-92.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1 (character-count limits identification)
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	4-5, A7-A12
	4b	Settings and locations where the data were collected	A2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6, A14
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	A2
	7b	When applicable, explanation of any interim analyses and stopping guidelines	6, A2
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5, A2-A3
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	A2-A3
Allocation	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers),	

concealment mechanism		describing any steps taken to conceal the sequence until interventions were assigned	5, A2-A3
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	4, A3
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7-8, A4
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8, A15, A18
	13b	For each group, losses and exclusions after randomisation, together with reasons	8, A18
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	A15
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8, A15, A18
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8-10, 21-23, Figure 1
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10, 25-26
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11-14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-14

Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	4, 14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.